(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 March 2002 (14.03.2002)

PCT

(10) International Publication Number
WO 02/19998 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US01/22621

(22) International Filing Date: 24 August 2001 (24.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/231,065 8 September 2000 (08.09.2000) US

(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BREIER, Alan** [US/US]; 11998 Woods Bay Court, Carmel, IN 46033 (US). **HEIMAN, Mark, Louis** [US/US]; 7523 Brookview Circle, Indianapolis, IN 46250 (US). **LEANDER, John, David** [US/US]; 8127 Groton Lane, Indianapolis, IN 46260 (US).

(74) Agents: **LENTZ, Nelsen, L.** et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DK, DK (utility model), DM, DZ, EC, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/19998 A2

(54) Title: A METHOD OF TREATING WEIGHT GAIN ASSOCIATED WITH ATYPICAL ANTIPSYCHOTIC USE

(57) Abstract: A method of treating weight gain associated with atypical antipsychotic use which comprises administering to a mammal in need thereof a therapeutically effective amount of N,N-dimethyl-1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride.

A METHOD OF TREATING WEIGHT GAIN ASSOCIATED WITH ATYPICAL ANTIPSYCHOTIC USE

Use of atypical antipsychotic agents is associated with weight gain in up to 50% of patients, a significant portion of the patient population. Weight gain is now a well documented side effect of treatment with olanzapine. Patients with schizophrenia are at risk for many health problems and weight gain increases the risk of obesity in these patients. Obesity is a leading cause of mortality as it frequently leads to conditions such as diabetes and cardiovascular disorders. It ranks second only to smoking as a leading cause of preventable death. Left untreated, this scenario could eventually produce insulin resistance and perhaps diabetes in addition to obesity. For patients who have been diagnosed with hypertension, weight gain only complicates treatment of this disorder. While dietary education and exercise can be used as part of the treatment program, this may not be sufficient intervention to prevent weight gain. In cases that are resistant to such lifestyle changes, drug intervention may be desired.

United States Patent No. 5,436,272, issued July 25, 1995 discloses a method of treating obesity in humans employing N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

In addition, International Patent Application WO 00/56313 published September 28, 2000 teaches a method of controlling weight gain associated with certain therapeutic drugs including atypical neuroleptics, such as olanzapine.

The present invention relates to a method for treating weight gain associated with atypical

antipsychotic use which comprises administering to a mammal in need thereof a therapeutically effective amount of a triple reuptake inhibitor of norepinephrine, serotonin and dopamine.

In addition, the present invention provides a method of treating weight gain associated with atypical antipsychotic use which comprises administering to a mammal in need thereof a therapeutically effective amount of N,N-dimethyl-1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride or a pharmaceutically acceptable salt or hydrate thereof.

The present invention further provides the use of N,N-dimethyl-1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride or a pharmaceutically acceptable salt or hydrate thereof for the manufacture of a medicament for treating weight gain associated with atypical antipsychotic use.

The preferred atypical antipsychotic for use in the present invention is olanzapine.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

The term "therapeutically effective" means an amount sufficient to attenuate weight gain associated with atypical antipsychotic use.

It will be understood that the dosage ranges for other animals will necessarily be quite different from the doses administered to humans, and accordingly that the dosage ranges described be recalculated. For example, a small dog may be only $1/10^{th}$ of a typical

human's size, and it will therefore be necessary for a much smaller dose to be used. The determination of an effective amount for a certain non-human animal is carried out in the same manner described below in the case of humans, and veterinarians are well accustomed to such determinations.

The essential feature of an atypical antipsychotic is less acute extrapyramidal symptoms, especially dystonias, associated with therapy as compared to a typical antipsychotic such as haloperidol. Clozapine, the prototypical atypical antipsychotic, differs from the typical antipsychotics with the following characteristics: (1) greater efficacy in the treatment of overall psychopathology in patients with schizophrenia nonresponsive to typical antipsychotics; (2) greater efficacy in the treatment of negative symptoms of schizophrenia; and (3) less frequent and quantitatively smaller increases in serum prolactin concentrations associated with therapy (Beasley, et al., Neuropsychopharmacology, **14**(2), 111-123 , (1996)).

As used herein, the term antipsychotic includes typical antipsychotics such as haliperidol and atypical antipsychotic such as olanzapine, risperidone, sertindole, Quetiapine,ziprasidone and clozapine.

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, and its preferrred crystal form II is a known compound and is described in U.S. Patent Nos. 5,229,382 and 5,736,541 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. It is understood that the present invention includes all pharmaceutically acceptable salts, hydrates, solvates, and polymorphs of olanzapine.

Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Patent

No. 3,539,573, which is herein incorporated by reference in its entirety. Clinical efficacy in the treatment of schizophrenia is described (Hanes, et al., Psychopharmacol. Bull., 24, 62 (1988)).

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Patent No. 4,804,663.

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Patent No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Patent Nos. 5,112,838 and 5,238,945. U.S. Patent Nos. 4,710,500; 5,112,838; and 5,238,945 .

Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,879,288, which is herein incorporated by reference in its entirety. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt.

Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Patent Nos. 4,831,031 and 5,312,925. Its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,831,031. U.S. Patent Nos. 4,831,031 and 5,312.

Triple reuptake inhibitors of norepinephrine, serotonin and dopamine preferably include compounds such as sibutramine (Meridia®). U. S. Patents 4,746,680 and 4,929,629 describes sibutramine and methods for making sibutramine and its monohydrate.

The use of sibutramine (N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3- methylbutylamine hydrochloride) in the treatment of depression is described in British Patent Specification 2098602 and the use of N,N- dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of Parkinson's disease is described in published PCT application WO 88/06444. US Patent No. 5,436,272 discloses the use of sibutramine for the treatment of obesity. A particularly preferred form of this compound is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate (sibutramine hydrochloride) which is described in US Patent 4,929,629. The term sibutramine includes racemates, enantiomers, solvates, hydrates and pharmaceutically acceptable salts thereof.

All of the U.S. patents which have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference.

Applicants have discovered, surprisingly, that sibutramine is effective in treating pharmacologically induced weight gain associated with atypical antipsychotic use.

In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-90% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oily suspensions. The excipients used in the preparation of these compounds are the excipients known in the pharmacists' art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

Compositions for the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example suppositories with cocoa butter or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions in aqueous and oily media or sterile solutions in a suitable solvent.

Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The therapeutically active compound sibutramine may be administered in any of the known pharmaceutical dosage forms, for example solid dosage forms such as tablets or capsules, or liquid dosage forms, for example those forms intended for oral or parenteral administration. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound to be administered will be in the range 0.1 to 50 mg preferably 1 to 30 mg per day given in one or more doses.

The ability of sibutramine to treat weight gain associated with atypical antipsychotic use may be demonstrated by the following studies.

In Vivo Study

Female Sprague Dawley rats were treated with either a placebo, olanzapine or a combination of olanzapine and either sibutramine or mazindol. Rats were fed a moderate carbohydrate, low fat diet. Fat utilization was measured after treatment. Results show that rats treated with a combination of olanzapine and sibutramine showed significantly less weight gain and showed higher fat consumption than olanzapine or the combination of olanzapine and mazindol.

Human Clinical Study

Patients who are treated with olanzapine for at least six months and experience significant weight gain (defined as greater than seven percent of baseline weight) are randomized to receive either sibutramine or a placebo. After six months, patients are evaluated for differences in weight gain and BMI (Body Mass Index).

WE CLAIM:

1. A method of treating weight gain associated with atypical antipsychotic use which comprises administering to a mammal in need thereof a therapeutically effective amount of N,N-dimethyl-1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride or a pharmaceutically acceptable salt or hydrate thereof.

2. A method of **Claim 1**, wherein N,N-dimethyl-1-[1-(4- chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride is administered in the form of its monohydrate.

3. A method of **Claim 1 or 2**, wherein the N,N-dimethyl-1-[1-(4- chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride is administered orally.

4. A method of **Claim 1**, wherein the N,N-dimethyl-1-[1-(4- chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride is administered parenterally.

5. A method of any one of **Claims 1 to 4**, wherein the N,N-dimethyl-1-[1-(4- chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride is administered in an amount of from about 0.1 to about 50 mg per day.

6. A method of **Claim 5**, wherein the amount is 1 to 30 mg per day.

7. A method of **Claim 6**, wherein the N,N-dimethyl-1-[1-(4- chlorophenyl) cyclobutyl]-3-methylbutylamine

hydrochloride is administered in an amount from 2.5 to 20mg per day.

8. A method of **Claim 7**, wherein the N,N-dimethyl-1-[1-(4- chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride is administered in an amount of about 10mg per day.

9. A method of any one of **Claims 1 to 9**, wherein the atypical antipsychotic is olanzapine.

10. A method of **Claim 9**, wherein the olanzapine is Form II.

11. A method of any one of **Claims 1 to 10**, wherein the N,N-dimethyl-1-[1-(4-chlorophenyl). cyclobutyl]-3-methylbutylamine hydrochloride is administered in conjunction with a pharmaceutically acceptable diluent or carrier.

12. Use of N,N-dimethyl-1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride or a pharmaceutically acceptable salt or hydrate thereof for the manufacture of a medicament for treating weight gain associated with atypical antipsychotic use.

13. A use of **Claim 12**, wherein N,N-dimethyl-1-[1-(4- chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride is administered in the form of its monohydrate.

14. A use of **Claim 12 or 13**, wherein the N,N-dimethyl-1-[1-(4- chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride is administered orally.

15. A use of **Claim 12**, wherein the N,N-dimethyl-1-[1-(4- chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride is administered parenterally.

16. A use of any one of **Claims 12 to 15**, wherein the N,N-dimethyl-1-[1-(4- chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride is administered in an amount of from about 0.1 to about 50 mg per day.

17. A use of **Claim 16**, wherein the amount is 1 to 30 mg per day.

18. A use of **Claim 17**, wherein the N,N-dimethyl-1-[1-(4- chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride is administered in an amount from 2.5 to 20mg per day.

19. A use of **Claim 18**, wherein the N,N-dimethyl-1-[1-(4- chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride is administered in an amount of about 10 mg per day.

20. A use of any one of **Claims 12 to 19**, wherein the atypical antipsychotic is olanzapine.

21. A use of **Claim 20**, wherein the olanzapine is Form II.